## REMARKS

Claims 1, 2 and 5-7 are pending in the application. In the present response, claim 1 has been amended. As provided below, support for the amendments to claim 1 is found throughout the specification as filed. It is believed that no new matter has been introduced.

Reconsideration and allowance of all of the pending claims, as amended, is respectfully requested.

Applicants gratefully acknowledge Examiner's consideration of the Information Disclosure Statement submitted May 24, 2007.

**35 U.S.C § 101 rejections**

Claims 1, 2, and 5- 7 remain rejected under 35 U.S.C § 101 because they are allegedly not supported by either a specific, substantial, and credible asserted utility and remain rejected under 35 U.S.C § 112, first paragraph as allegedly failing to comply with the enablement requirement.

According to the Office Action, all the claims, including claim 7, are being examined as methods for detecting differential expression of GPR49 polypeptide in colon cancer. The Office Action indicates that the invention elected for examination is of a method of detecting the levels of the polypeptide encoded by a colon cancer gene, GPR49 (SEQ ID NO:84). (See page 2 of the Office Action.) The Office Action suggests that the specification discloses GPR49 mRNA over-expression associated with colon cancer, but is silent with respect to the levels of GPR49 polypeptide expression. The Office Action acknowledges the Declaration submitted by Dr. Martinez, which states that elevated levels of GPR49 mRNA are expected to produce elevated levels of GPR49 protein, but appears to conclude that no data or other objective evidence was provided in the declaration to support the overexpression of GPR49 polypeptide in colon cancer. (See page 3 of the Office Action.)

The Office Action further indicates that there is no real world utility for the method as claimed because the art recognizes that there is no correlation between mRNA expression and polypeptide expression. The Office Action cites Brennan (J. Autoimmun. 1989, 2:177-186), Zimmer (Cell Motil. Cytoskeleton 199, 20:325-337), Powell (Pharmacogenetics 1998, 8:411-421), Hell (Lab. Invest. 1995, 73:492-496),

Carrere (Gut, 1999, 44:545-551), Guo (J. Pharmacol. Exp. Ther. 2002, 300:206-212) and Jang (Clin. Exp. Metastasis 1997, 15:469-483) to support the allegation that mRNA expression levels do not necessarily correlate with protein expression levels. Specifically, Brennan was cited as apparently teaching that while high levels of TNF alpha mRNA were detected, TNF alpha protein was undetectable. Zimmer was cited as apparently teaching that there is no correlation between the mRNA and protein levels of calcium-modulated protein S100 alpha. Powell was cited for apparently teaching that P450 E1 mRNA levels and protein levels do not correlate. Hell was cited for apparently teaching that there is no correlation between bcl-2 mRNA levels and Bcl-2 protein levels. Carrere was cited for apparently teaching an absence of correlation between protein and mRNA levels for the Reg protein. Guo was cited for apparently teaching that Oatp2 mRNA levels do not show correlation with Oatp2 protein levels. Finally, Jang was cited as apparently teaching that it is not known if changes in protein levels track with changes in mRNA levels for metastasis-associated genes. The Office Action, therefore, concludes that the claims lack specific, substantial, and credible asserted utility without objective evidence that indicates that differential expression of GRP49 protein in colon cancer tissue when compared to normal colon tissue.

According to the MPEP § 2107.02 "[a]s a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." Applicants submit that the specification discloses the use of GPR49 polypeptide to diagnose colon cancer.

The fact that Brennan, Zimmer, Powell, Hell, Carrere, Guo and Jang teach that the level of expression of certain proteins does not correlate with mRNA levels does not mean that the same is true for GPR49. To further support the Applicants' arguments, Applicants present herewith Exhibit A, an article by McClanahan et al. (Cancer Biol. Ther. 2006, 5:419-426). This article clearly teaches correlation of GPR49 mRNA and protein expression levels in colon cancer tissues. For example, the Abstract reads "...overexpression of GPR49 in tumor tissues was further illustrated by specific immunohistochemical staining of ...a finding that correlates with the mRNA expression of the receptor." At page 423, second column, the authors state "[i]n addition to mRNA

upregulation, GPR49 protein was immunohistochemically detected in primary colon...tissues and was absent or very weakly detected in the corresponding non-cancerous tissues." This article provides objective evidence that GPR49 mRNA and polypeptide are differentially expressed in colon cancer tissue when compared to normal colon tissue. Thus, the instant claims have specific, substantial, and credible asserted utility.

In view of the above comments, withdrawal of the 35 U.S.C. § 101 rejection for lack of utility is respectfully requested.

**35 U.S.C § 112, first paragraph rejections**

Claims 1, 2 and 5- 7 remain rejected under 35 U.S.C § 112, first paragraph as allegedly lacking enablement.

According to the Office Action, the specification is enabling for a method of diagnosing colon cancer by detecting differential expression of GPR49 mRNA in the test sample. The Office Action appears to conclude, however, that without objective evidence to indicate differential expression of GPR49 protein in colon cancer tissue when compared to normal colon tissue, one skilled in the art would be forced to do a large amount of undue experimentation before being able to practice the claimed invention. The Office Action concludes that submission of objective evidence demonstrating differential expression of GPR49 protein in a colon cancer sample compared to a normal control would overcome this rejection. (See page 6 of the Office Action.)

As mentioned above, Exhibit A, the article by McClanahan et al. teaches correlation of GPR49 mRNA and protein expression levels in colon cancer tissues. To further support Applicants' contentions, Applicants offer this objective evidence to demonstrate differential expression of GPR49 protein in a colon cancer sample compared to a normal control.

In view of the above comments, withdrawal of the 35 U.S.C. § 112, first paragraph rejection for lack of enablement is respectfully requested.

**35 U.S.C § 112, second paragraph rejections**

Claims 1, 2 and 5- 7 remain rejected under 35 U.S.C § 112, second paragraph allegedly for being vague and indefinite.

According to the Office Action, the claims are vague and indefinite because they recite "GPR49" as the sole means of detecting and comparing the levels of polypeptide referred to in claims 1 and 7.

Simply in order to advance prosecution, the claims have been amended to recite a method of diagnosing or monitoring colon cancer in a subject by comparing the level of G protein-coupled receptor 49 (GPR49) polypeptide in the subject with a control level of GPR49 polypeptide. Support for this amendment is found throughout the specification as filed. For example, at page 16 of the specification as filed, paragraph [0118] defines GPR49 and Table 3 lists GPR49 as a receptor.

In view of the above amendments, withdrawal of the 35 U.S.C. § 112, second paragraph rejections is respectfully requested.

## CONCLUSION

In view of the above amendments and remarks Applicants respectfully submit that the rejections of record have been overcome, and the pending claims are now in form of allowance. Allowance of the application on the merits is respectfully requested.

A request for continued examination (RCE) and a petition for a three-month extension of time to file this response accompany this paper.

During the pendency of this application please treat any reply requiring a petition for extension of time for its timely submission as containing a request therefore for the appropriate length of time. The Commissioner is hereby authorized to charge all required extension of time fees during the entire pendency of this application to Deposit Account No. 01-1425.

If any outstanding issue remains, the Examiner is invited to contact the undersigned agent for a discussion of a mutually agreeable solution.

Maria Restrepo-Hartwig
Agent for Applicants
Reg. No. 52,163

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940
Tel. No. (973) 660-6383